Effect of second primary cancer on the prognosis of patients with non-small cell lung cancer

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Background: Second primary cancer (SPC) is not a rare event for patients with non-small cell lung cancer (NSCLC), especially for those who survive for a longer period of time. This study was aimed to explore the effects of SPC on the survival of NSLCL patients.

Methods: A total of 241,805 patients with primary NSCLC were identified between 2004 and 2014 from the Surveillance, Epidemiology, and End Results (SEER) database. The incidence of SPC and its effect on the overall survival (OS) and lung cancer-specific survival (LCSS) was explored and analyzed using Cox regression model with SPC being treated as a time-dependent covariate.

Results: The incidence of SPCs after the diagnosis of NSCLC was 6.4%, with the second primary lung cancer being the most common one (45.1%). About half of the SPCs (50.7%) occurred during the first year after the diagnosis of NSCLC. It seemed that patients who developed SPC late in the follow-up period tended to have poor prognosis. Multivariable analysis with Cox regression showed that the occurrence of SPC was a poor prognostic factor for patients with NSCLC [hazard ratio (HR), 1.298; 95% confidence interval (CI), 1.270–1.326; P=0.000], and it increased the risk of LCSS (versus no SPC, HR, 1.094; 95% CI, 1.066–1.123; P=0.000).

Conclusions: The occurrence of SPC after the diagnosis of NSCLC was not a rare event, and it indicated a poorer prognosis compared with patients without it. During the follow-up, attention should be paid to the screening of SPC especially the second primary lung cancer, and a rational surveillance policy should be formed and implemented.

Keywords: Non-small cell lung cancer (NSCLC); second primary cancer (SPC); Surveillance, Epidemiology, and End Results database (SEER database); overall survival (OS); lung cancer-specific survival (LCSS)

Introduction

Lung cancer remains the leading cause of cancer deaths around the world, and with the highest incidence are non-small cell lung cancers (NSCLCs) (1). With the improvement of diagnostic tools and the progress of treatment, more and more patients with NSCLC are surviving for a longer period of time ; thus, the chance of developing another cancer has become more and more prominent, which is distinguished from metastasis of the initial primary cancer (2,3).

Studies indicated that the incidence of multiple primary cancers (MPCs) ranges from 0.9% to 26.3% (2-7). Most of these studies focused on MPCs prior and after lung cancer and several researches had reported on the

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incidence of second primary cancers (SPCs) in NSCLC patients (8,9). However, up till present day, there are few studies that focused on SPC in NSCLC patients by using the Surveillance, Epidemiology, and End Results (SEER) database.

The aim of this study was to explore the incidence of SPCs in NSCLC patients by using the SEER database of the National Cancer Institute (NCI), and to investigate its effects on the survival of these patients.

Methods

We collected data in the SEER program of the NCI which covered approximately 28% of the US population (10). We used SEER*Stat version 8.3.4 software to extract data from the SEER database. This study was approved by the review board of our institute.

The selection criteria included patients who pathologically confirmed NSCLC between 2004 and 2014. For further refined screening, we selected patients with adenocarcinoma (SEER codes 8140, 8250, 8252–8255, 8260, 8310, 8323, 8480, 8481, 8490, 8570, 8574), squamous cell carcinoma (SEER codes 8052, 8070, 8074, 8083, 8084), large cell carcinoma (SEER codes 8012, 8013), and adenosquamous carcinoma (SEER code 8560). Patients with previous malignant diseases were excluded, and as well as patients without detailed information about SPC. Ultimately, 241,805 patients were included in this study.

The data that was extracted for this study included age, sex, race, marital status, if SPC occurred, histology, differentiation, surgical procedure, TNM stage [based on the criteria of the 6th edition of the American Joint Committee on Cancer (AJCC)], survival time, radiation and chemotherapy status. Age was grouped into four categories (≤60, 61–70, 71–80, and >80 years) in the following analyses. We classified surgical procedures into six groups: no surgery; sub-lobectomy (including local tumor destruction, excision or resection of less than one lobe such as wedge resection and segmentectomy); lobectomy (including lobe or bilobectomy); pneumonectomy; surgery (the type of operation is unclear), and unknown. Local tumor destruction included laser ablation or cryosurgery, electrocautery, fulguration (include the use of hot forceps for tumor destruction).

The criteria for multiple primary malignancies in the SEER registry were applied for those that were first proposed by Warren and Gates (11): each of the tumors must present a definite histologic picture of malignancy; each must be distinct; and if the probability that one was a metastatic lesion different from the other then must be excluded. Immunohistochemical staining was performed using cancer site specific antibodies if necessary (12).

The standards diagnosis of multiple primary lung cancer were as the following (13): tumors at different sites (for example, a tumor in a lung and another separate tumor in the trachea) or pathology; a single tumor in each lung; tumors diagnosed more than three years apart; an invasive tumor following an *in situ* tumor more than 60 days after the abstracted diagnosis as multiple primaries unless stated or proven to be metastatic; when it is not possible to determine if there is a single tumor or multiple tumors, abstract as a single primary; and tumors that do not meet any of the above criteria are a single primary. For cancers involving multiple organs, the diagnostic criteria for MPC are the same as indicated by Warren and Gates.

Statistics

The endpoint of this study was the overall survival (OS) and the lung cancer-specific survival (LCSS). The OS is the time interval from the initiation of the diagnosis of NSCLC to the death of patient from any causes. The LCSS is defined as the time interval from the diagnosis of NSCLC to the death from the primary NSCLC; and the death from any other causes is treated as censored. The association between variables was analyzed by either Chi-square test or Mann-Whitney and Wilcoxon test. Survival curve was generated using Kaplan-Meier method and the difference was examined using log-rank test. Cox regression analysis was performed to explore the significant predictors for OS and the hazard ratio (HR) of the prognostic factor was estimated. Because the time interval from the diagnosis of NSCLC to the occurrence of SPC varied among patients, so we examined the HR of SPC for patients who suffered from SPC within 6, 12, 36, 60 and 120 months, respectively. In the final Cox regression model, SPC was treated as a time-dependent covariate.

All statistical analyses were performed by SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA) and Stata/MP 14.0 for Windows (StataCorp LP, College Station, TX, USA). And a probability value less than 0.05 was considered to be significant.

Results

The patient cohort (n=241,805) in this study consisted of

Table 1 Demographics and clinical characteristics of patients selected

Factors	No SPC (%)	SPC (%)	P value
Total	226,374 (93.6)	15,431 (6.4)	
Gender			0.009
Female	104,358 (93.5)	7,281 (6.5)	
Male	122,016 (93.7)	8,150 (6.3)	
Race			0.000
White	180,806 (93.3)	13,054 (6.7)	
Black	27,420 (94.6)	1,554 (5.4)	
Others	18,148 (95.7)	823 (4.3)	
Age			0.000
≤60	57,272 (95.0)	3,029 (5.0)	
61–70	70,855 (92.6)	5,689 (7.4)	
71–80	67,280 (92.8)	5,239 (7.2)	
>80	30,967 (95.5)	1,474 (4.5)	
Differentiation			0.000
Well	13,196 (88.6)	1,699 (11.4)	
Moderate	48,311 (90.5)	5,076 (9.5)	
Poor	64,400 (93.3)	4,654 (6.7)	
Undifferentiated	3,622 (93.6)	247 (6.4)	
Unknown	96,845 (96.3)	3,755 (3.7)	
Histology			0.000
Squamous	71,872 (93.8)	5,214 (6.2)	
Adenocarcinoma	139,336 (93.8)	9,220 (6.2)	
Others	15,166 (93.8)	997 (6.2)	
T-stage			0.000
T0	967 (96.4)	36 (3.6)	
T1	41,558 (87.9)	5,741 (12.1)	
T2	65,352 (92.1)	5,617 (7.9)	
T3	13,844 (95.0)	731 (5.0)	
T4	82,018 (97.0)	2,555 (3.0)	
Tx	22,635 (96.8)	751 (3.2)	
N-stage			0.000
N0	87,474 (89.7)	10,087 (10.3)	
N1	19,684 (93.2)	1,425 (6.8)	
N2	76,322 (96.5)	2,739 (3.5)	
N3	25,935 (97.4)	696 (2.6)	
Nx	16,959 (97.2)	484 (2.8)	

Table 1 (continued)

Table 1 (continued)

Factors	No SPC (%)	SPC (%)	P value
M-stage			0.000
M0	118,470 (90.4)	12,532 (9.6)	
M1	99,611 (97.5)	2,558 (2.5)	
Mx	8,293 (96.1)	341 (3.9)	
Marriage			0.000
Married	116,431 (93.1)	8,681 (6.9)	
Others	109,943 (94.2)	6,750 (5.8)	
Radiation			0.000
Radiation	88,876 (95.3)	4,377 (4.7)	
Others	137,498 (92.6)	11,054 (7.6)	
Chemotherapy			0.000
Yes	100,570 (94.8)	5,569 (5.2)	
Others	125,804 (92.7)	9,862 (7.3)	
Surgical procedure			0.000
No	166,989 (96.6)	5,894 (3.4)	
Sublobectomy	11,430 (86.2)	1,827 (13.8)	
Lobectomy	42,853 (85.5)	7,272 (14.5)	
Pneumonectomy	3,393 (90.5)	356 (9.5)	
Surgery (the type of operation is unclear.)	537 (91.8)	48 (8.2)	
Unknown	1,172 (97.2)	34 (2.8)	
Survival			0.000
Alive	56,200 (89.9)	6,301 (10.1)	
Dead	170,174 (94.9)	9,130 (5.1)	

NSCLC, non-small cell lung cancer; SPC, second primary cancer.

130,166 males (53.8%) and 111,639 females (46.2%) with median age of 68.1 years (range, 5–105 years). The last follow-up time was December 2014, and mean follow-up time was 20 months (range, 0–131 months). During the follow up period, 179,304 (74.2%) patients died and median OS was 9 months. A total of 15,431 (6.4%) suffered from SPCs during the follow-up. The clinical characteristics of these patients are shown in *Table 1*.

About half of the SPCs (50.7%) occurred during the first years after the diagnosis of NSCLC (*Figure 1A*). However, the incidences of SPC for the survived patients differed a little each year during the follow-up, fluctuating between
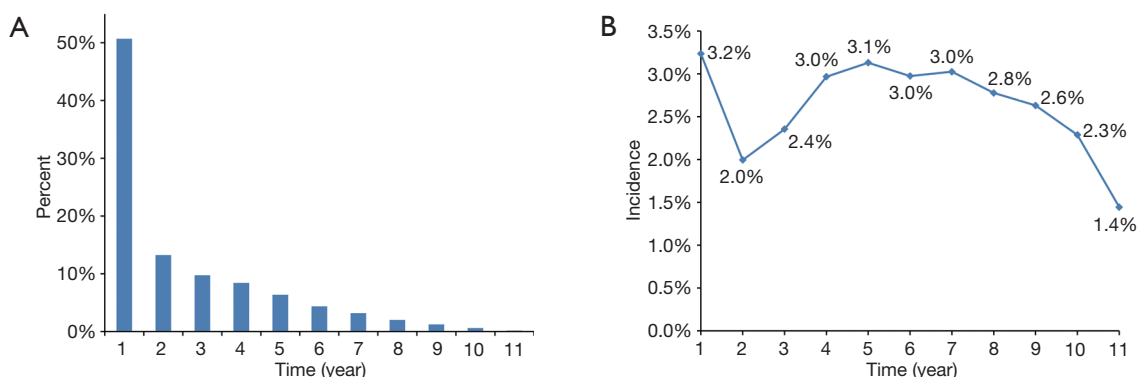
Figure 1 The distribution and the incidence of SPC after established diagnosis of NSCLC over time. (A) The distribution of the observed SPC over time after the diagnosis of NSCLC; (B) the incidence of SPC in survived patients after the diagnosis of NSCLC during a given year. NSCLC, non-small cell lung cancer; SPC, second primary cancer.
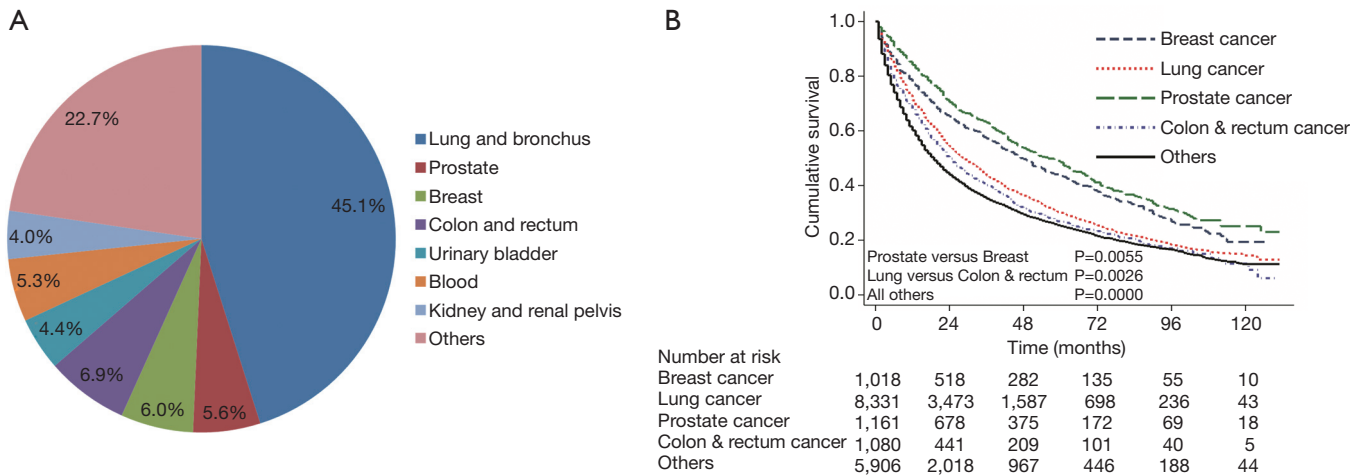

Figure 2 Common sites of SPCs and the survival curve of different SPCs. (A) Common sites of SPCs and their percentage; (B) survival curves of different SPCs. SPC, second primary cancer.

1.4% and 3.2% (*Figure 1B*). The median time interval from the diagnosis of NSCLC to the occurrence of SPC was 12 months (range, 0–128 months).

The most common SPC was lung cancer (45.1%), and the second one was colon and rectum cancer (6.9%), which was followed by prostate cancer (5.6%) and breast cancer (6.0%) (*Figure 2A*). The prognosis of patients suffered from prostate or breast cancer after diagnosis of NSCLC was better than those who suffered from the second primary lung cancer or colon and rectum cancer (median survival after diagnosis of SPC was 56, 48, 29 and 24 months for prostate cancer, breast cancer, lung cancer and colon and rectum cancer, respectively) (*Figure 2B*).

Patients with SPCs seemed to present a more favorable

prognosis than those without SPCs (median survival 59 versus 13 months, P=0.000) (*Figure 3*). However, only those who survived for a period of time have the chance to suffer from SPC; thus, the interval from the time of diagnosis of NSCLC to the occurrence of SPC would be an immortal time bias. In order to reduce the immortal time bias, we compared patients' survival who suffered from SPC during the first year, the third year, the fifth year and the ninth year after the diagnosis of NSCLC with those who survived to the same year without SPC. Results showed that patients who suffered from SPC were apt to have a poor prognosis as the time interval increases (*Figure 4A,B,C,D*).

In the multivariable analysis with Cox regression model, we examined the HR for SPC after controlling confounders
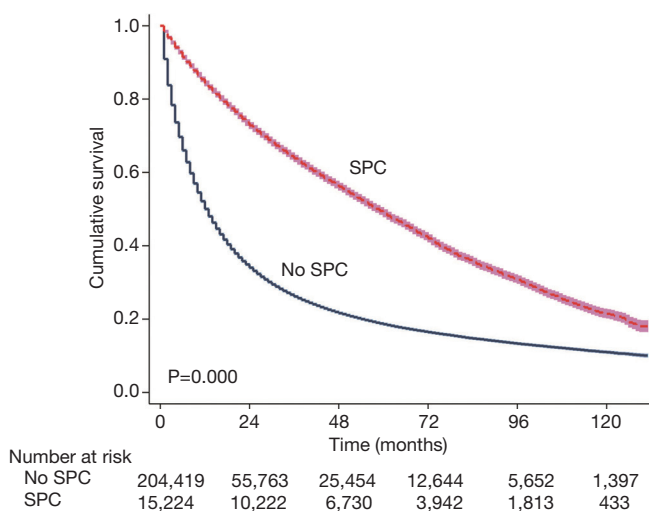
Figure 3 Overall survival and 95% confidence interval for NSCLC patients with or without SPCs. The median survival time for patients with SPC and those without SPC were 59 and 13 months, respectively. SPC, second primary cancer; NSCLC, non-small cell lung cancer.

in patients who suffered from SPC within 6, 12, 36, 60 and 120 months, respectively. There was a persistent decline in HR with the increment of time span, from the time of diagnosis of NSCLC to the occurrence of SPC (HR diminished from 0.883 for those who suffered from SPC within 6 months, to 0.629 for those who suffered from SPC within 120 months) (*Table 2*). The proportional hazard hypothesis for SPC was false; thus, the final Cox regression model was fitted with SPC being treated as a time-dependent covariate. Our results showed that the occurrence of SPC was an adverse prognostic factor for patients with NSCLC [HR, 1.298; 95% confidence interval (CI), 1.270–1.326; P=0.000], and at the same time it increased the risk of LCSS (HR, 1.094; 95% CI, 1.066–1.123; P=0.000) (*Table 3*). Other significant prognostic factors for OS and LCSS included gender, age, differentiation, histology, TNM-stage, radiation, chemotherapy, and surgical procedure.

Discussion

With the advanced development in the diagnosis and treatment methods, many patients with NSCLC tend to have the chance to survive for a longer period of time. The occurrence of SPC in NSCLC patients, especially for long time survivors, is not a rare event. Several researches about SPC have been performed, focusing on the incidence, risk

factors and survival and the incidence of SPC which ranged from 1.7% to 7.3% (3,4,6,8).

A study using data from SEER database between 1973 and 2003 by Hayat *et al.* had demonstrated the incidence of MPCs, which occurred before or after the primary lung cancer and it was 9% (14). In our current study, the incidence of SPC after NSCLC was lower than Hayat *et al.*, and the probable reason might be because we excluded patients with history of malignant disease. The highest morbidity of SPCs after the diagnosis of NSCLC was lung cancer (45.1%), which might be due to the risk factors that cause lung cancer still exist (15). The second most common SPC was prostate cancer followed by colon and rectum cancer, which was similar to the incidence of these cancers in the general population (1). The survival time after the occurrence of prostate cancer was better than in breast cancer patients, followed by second primary lung, colon and rectum cancer. It was just similar to those who suffered from these cancers as their unique primary cancer (1). Similar to previous studies (4,6), about 50% of all SPCs occurred during the first year after the diagnosis of NSCLC. However, the incidence of SPC during each year after NSCLC being diagnosed had changed slightly, from 3.2% to1.4%. The findings indicate that attention should be paid more to the occurrence of SPC during all the follow-up period after the diagnosis of NSCLC.

The effect of SPC on the survival has been explored in several previous studies. In a retrospective study by Duchateau and Stokkel (3), multi-primary cancers either in their history or in the follow-up period were evaluated in 860 patients with NSCLC. The 5-year survival rate in patients with a second tumor in the follow-up period was better than in patients without any other second tumor (P=0.029). They speculated that patients with two or more cancers are predisposed to have rather slow progression tumors. However, we believe, only those who survived long enough had the opportunity to suffer from another primary cancer and this might inflicted the bias on the results favoring those with SPC.

In another retrospective study by Aguilo *et al.* (2), the OS of 1,686 patients with lung cancer as unique primary malignancy was compared with 228 patients who suffered from lung cancer and another independent primary cancer. Their results showed that patients with multiple cancers presented a slightly better survival rate than in patients with lung cancer as a unique primary cancer. They speculated that a second independent cancer should be considered as
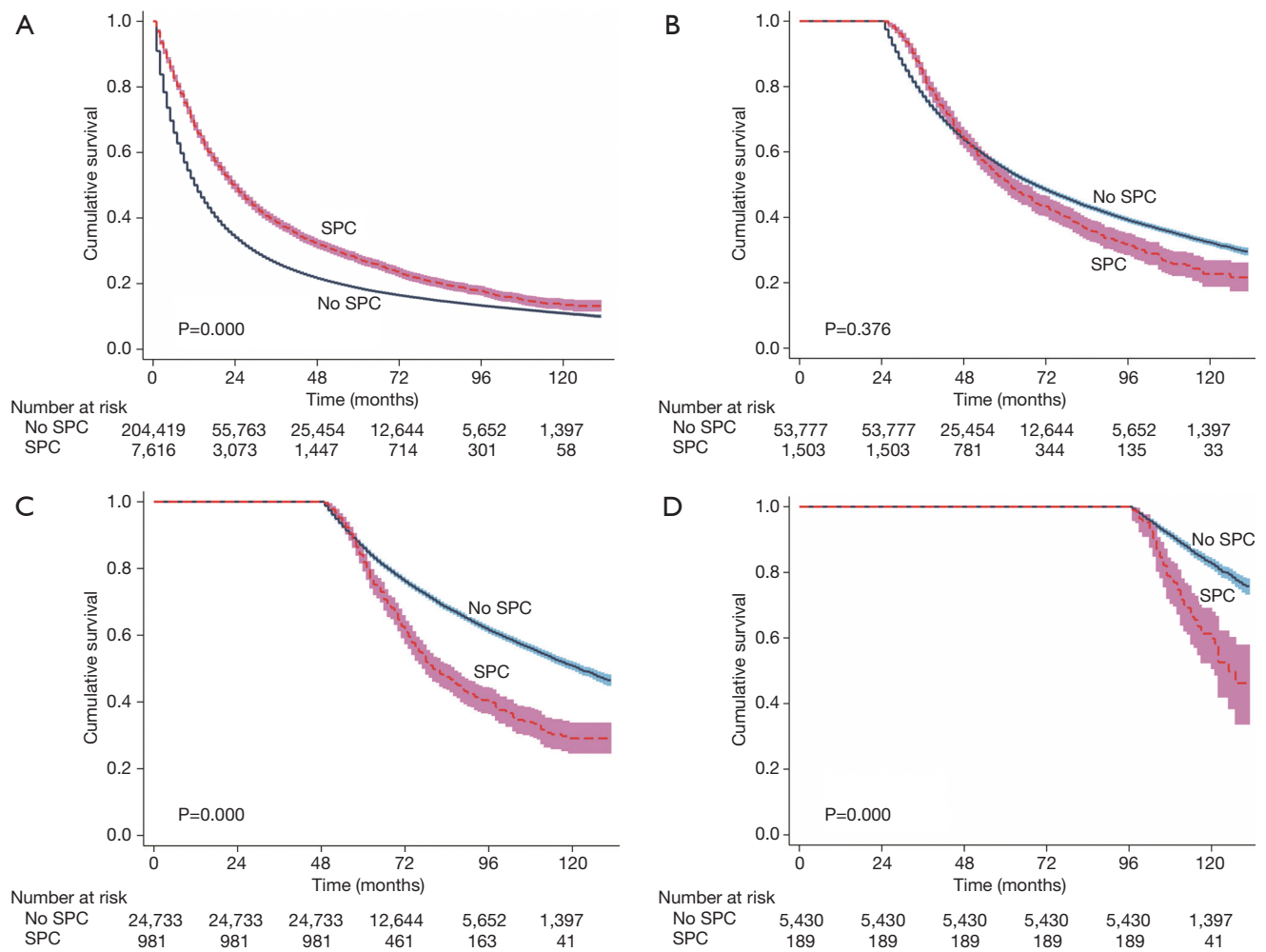
Figure 4 Overall survival and 95% confidence interval of patients suffering from SPCs at a given time period after the diagnosis of NSCLC compared with those who survived to that period without SPC. (A) The overall survival and 95% confidence interval of patients suffering from SPCs during the first year after diagnosis of NSCLC compared with all patients without SPCs; (B) the overall survival and 95% confidence interval of patients suffering from SPCs during the third year after the diagnosis of NSCLC compared with all patients without SPCs; (C) the overall survival and 95% confidence interval of patients suffering from SPCs during the fifth year after the diagnosis of NSCLC compared with all patients without SPCs; (D) the overall survival and 95% confidence interval of patients suffering from SPCs during the ninth year after the diagnosis of NSCLC compared with all patients without SPCs. NSCLC, non-small cell lung cancer; SPC, second primary cancer.

a separate entity in terms of prognosis and treatment. It seems that both cancers barely interact, and that it is the cancer with worst prognosis is the one which ultimately determines the outcome.

In this current study, with the exclusion of patients with previous malignant disease, the median survival time for patients with SPC was longer than those without SPC (59 months for SPC versus 13 months for no SPC, P=0.000) (*Figure 3*). Our results were similar to the previous studies

(2,3,5). However, the time interval from the diagnosis of NSCLC to the occurrence of SPC was an immortal time during the survival analysis and it biased the results (16). In order to reduce the immortal time bias, we compared patients' survival who suffered from SPC during the first year, the third year, the fifth year and in the ninth year after the diagnosis of NSCLC with those who survived to the same year without SPC (*Figure 4A,B,C,D*). For patients with synchronous SPC (occurrence at 0-6 months

Table 2 Cox regression analysis for the overall survival of NSCLC patients with SPC occurrence at different period

SPC or not	Event (%)	HR	95% CI	P
No SPC	170,174 (75.2)	–	–	–
SPC at different time interval				
0–6 months	4,439 (67.2)	0.883	0.857–0.910	0.000
0–12 months	5,209 (66.6)	0.858	0.834–0.882	0.000
0–36 months	7,229 (63.6)	0.751	0.734–0.769	0.000
0–60 months	8,389 (61.4)	0.689	0.674–0.705	0.000
0–120 months	9,122 (59.2)	0.629	0.615–0.642	0.000

NSCLC, non-small cell lung cancer; SPC, second primary cancer; HR, hazard ratio; CI, confidence interval.

Table 3 Cox proportional hazard regression analysis for the overall survival and lung cancer-specific survival of SCLC patients with SPC being treated as a time-dependent covariate

Factors	OS			LCSS		
	HR	95.0% CI	P	HR	95.0% CI	P
Male (versus female)	1.241	1.229–1.253	0.000	1.212	1.200–1.225	0.000
Race (versus White)						
Black	0.987	0.973–1.001	0.065	0.973	0.958–0.988	0.000
Others	0.756	0.742–0.769	0.000	0.744	0.729–0.758	0.000
Age (versus ≤60)						
61–70	1.098	1.084–1.112	0.000	1.070	1.056–1.084	0.000
71–80	1.247	1.231–1.263	0.000	1.179	1.163–1.196	0.000
>80	1.382	1.360–1.404	0.000	1.289	1.276–1.312	0.000
Differentiation (versus well differentiation)						
Moderate	1.344	1.310–1.379	0.000	0.642	0.625–0.660	0.000
Poor	1.572	1.533–1.612	0.000	0.882	0.869–0.895	0.000
Undifferentiated	1.654	1.582–1.728	0.000	1.049	1.037–1.062	0.000
Unknown	1.504	1.467–1.542	0.000	1.101	1.057–1.146	0.000
Histology (versus squamous cell carcinoma)						
Adenocarcinoma	0.934	0.924–0.944	0.000	0.903	0.884–0.923	0.000
Others	1.076	1.055–1.098	0.000	0.867	0.849–0.885	0.000
T–stage (versus T0)						
T1	0.759	0.707–0.815	0.000	0.833	0.773–0.898	0.000
T2	1.103	1.029–1.184	0.006	0.586	0.573–0.600	0.006
T3	1.416	1.318–1.521	0.000	0.927	0.909–0.945	0.000
T4	1.485	1.385–0.593	0.000	1.214	1.183–1.245	0.000
Tx	1.181	1.100–1.268	0.000	1.260	1.238–1.283	0.000

Table 3 *(continued)*

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Table 3 (continued)

Factors	OS			LCSS		
	HR	95.0% CI	P	HR	95.0% CI	P
N–stage (versus N0)						
N1	1.361	1.337–1.386	0.000	0.701	0.685–0.716	0.000
N2	1.483	1.464–1.502	0.000	1.008	0.982–1.034	0.566
N3	1.490	1.465–1.516	0.000	1.093	1.070–1.116	0.000
Nx	1.370	1.342–1.399	0.000	1.093	1.067–1.119	0.000
M–stage (versus M0)						
M1	1.793	1.774–1.814	0.000	0.932	0.905–0.960	0.000
Mx	1.063	1.034–1.092	0.000	1.780	1.730–1.831	0.000
Other marriage status (versus married)	1.096	1.085–1.107	0.000	1.078	1.067–1.089	0.000
No radiation or unknown (versus radiation)	1.135	1.123–1.146	0.000	0.898	0.888–0.908	0.000
No chemotherapy or unknown (versus chemotherapy)	1.910	1.890–1.931	0.000	0.532	0.526–0.538	0.000
Surgery (versus no surgery)						
Sublobectomy	0.431	0.420–0.442	0.000	1.217	1.139–1.301	0.000
Lobectomy	0.285	0.280–0.290	0.000	0.491	0.457–0.528	0.000
Pneumonectomy	0.405	0.388–0.422	0.000	0.312	0.291–0.334	0.000
Surgery, NOS	0.464	0.420–0.511	0.000	0.467	0.431–0.507	0.000
Unknown	0.830	0.781–0.883	0.000	0.568	0.501–0.644	0.000
SPC* (versus no SPC)	1.298	1.270–1.326	0.000	1.094	1.066–1.123	0.000

*, being treated as a time-dependent covariate. NSCLC, non-small cell lung cancer; SPC, second primary cancer; HR, hazard ratio; CI, confidence interval; OS, overall survival; LCSS, lung cancer-specific survival.

after diagnosis of NSCLC), a better prognosis was noted than those without SPC (*Table 2*), which is similar to the findings by Aguilo *et al.* (2). Patients with SPC were apt to have a poor prognosis with the increment of time interval between NSCLC and SPC. The reasons underlying the findings were unclear. However, with the increment of the time interval between NSCLC and SPC, patients with and without SPC inclined to be balanced with their baseline characters; however, more studies are needed regarding this issue.

In this study, Cox regression analysis was used to examine the HR of SPC, which occurred within 6, 12, 36, 60 and 120 months, respectively. Results showed that the HR decreased as the time span increased. The results indicated a false proportional hazard hypothesis; thus, a time-dependent Cox regression model was fitted with SPC being treated as a time-dependent covariate (17).

Unlike the previous studies, in this current study SPC had demonstrated a significant prognostic factor detrimental to the survival in the Cox regression analysis (HR, 1.298; 95% CI, 1.270–1.326; P=0.000). To our knowledge, this is the first time to establish the adverse effects of SPC on the survival of NSCLC patients.

Different to our analysis, Donin *et al.* (18) analyzed cancer data of the SEER database from another aspect. They examined mortality that is attributable to first and second primary malignancies, and concluded that a significant proportion of cancer survivors will develop and die from lung cancer, which is consistent with the known epidemiology of lung cancer that it is the leading cause of cancer-related death in the world (1). Different from their research aspect, we studied the effect of SPC on the OS and LCSS of patients and concluded that the occurrence of SPC increased the risk of OS (29.8%) and LSCC (9.4%)

separately for patients with NSCLC. Obviously, it has a much greater risk of non-LCSS death than the no SPC patients, but the reason is not entirely clear. However, NSCLC patients' immunity might be influenced by SPC, which might result in more deaths.

Since the incidence of SPC is high and it affects patients' survival with lung cancer, it is suggested that we should pay more attention to the screening of SPCs, especially second primary lung cancer. According to the NCCN guidelines for lung cancer screening (19), it is suggested that a history of prior lung cancer places an individual at higher risk for the development of a second lung cancer, irrespective of age and smoking history, and all lung cancer patients should be screened for second primary lung cancer. But, the information about the methods of screening of SPC is absent in the SEER database.

There are several potential limitations in our study that should be considered. Firstly, the presence of the heterogeneity of the population and the retrospective setting of this study is one of the limitations. Secondly, the SEER database itself is a limitation since it is an observational data that may engender inaccurate results (20). Thirdly, there was no information regarding comorbidities, targeted therapy, neoadjuvant therapy, and immune therapy in SEER database. This may have caused a certain bias in our results. Fourthly, the performance status and comorbidities of patients was unknown, which may have also affected the interpretation of our findings.

In conclusion, this study, despite the presence of several limitations, with the large number of patients had demonstrated the adverse effects of SPC on the survival rate using time-dependent Cox regression analysis. Attention should be paid to the screening of SPCs, especially the second primary lung cancer during the follow-up period. It is imperative that further investigations are needed to advance our understanding and to enable the development of effective measures against SPCs.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by Ethics Committee of Beijing Huaxin Hospital {[2018] ethical approval (37)}.

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